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Original Article

Subjective sleep and overall survival in chemotherapy-naïve patients with metastatic colorectal cancer

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ABSTRACT

Backround: Sleep disorders are prevalent in patients with advanced cancer. Their impact on clinical outcomes is not well understood.
Methods: A post-hoc analysis was conducted in 361 chemo-naïve patients with metastatic colorectal cancer completing twice the EORTC QLQ-C30 questionnaire within a randomized international phase III trial. The study assessed the effect on overall survival (OS) of subjective sleep complaint, used as a normal or a time-dependent covariate (TDC), using a multivariate Cox proportional hazard model. Prognostic analysis was conducted on the whole study population and separately in each treatment arm (conventional FOLFOX2, or chronomodulated chronoFLO4).
Results: Sleep problems were reported by 202 patients (56%) at baseline and by 188 (52%) on treatment. Sleep problems at baseline were independently associated with a higher risk of earlier death (HR: 1.36; p = 0.011), progression (HR: 1.43; p = 0.002) and poor treatment response (RR: 0.58; p = 0.016). TDC analysis confirmed the independent prognostic effect of sleep problems on OS (HR: 1.37; p = 0.008), while on treatment this effect was only observed using univariate analysis. The negative prognostic value of sleep problems on OS at baseline, on treatment, and as a TDC was greatest on chronoFLO4 compared to FOLFOX2.
Conclusions: Subjective sleep problems are associated with poor clinical outcomes in metastatic colorectal cancer patients and affect chronotherapy effectiveness. There is a need for a well-tuned circadian timing system in order to increase chronotherapy activity. Prospective studies are needed for determining the impact of therapeutic approaches on sleep disorders upon quality of life and survival of cancer patients.

1. Introduction

Sleep problems are prevalent in cancer patients and survivors, with nearly two-thirds of patients reporting them [1–4]. However, relatively little is known about sleep disorders in colorectal cancer patients. In a study of 157 adults with colon or rectal cancer, sleep problems were reported by 35% of them, and higher levels of sleep problems predicted for more fatigue, together with more depression and poorer performance status [5]. In another small study involving 21 patients with colorectal cancer undergoing adjuvant chemotherapy, clinically significant sleep disturbances were observed [6]. Berger et al. also noted substantial evidence of circadian disruption in their sample, suggesting that patients diagnosed with these types of cancer experience lack of distinction between nighttime and daytime in their activities [6]. This phenomenon was previously described by patients with advanced cancers, where substantial amounts of time spent asleep during the day and awake during the night effectively blur the line between day and nighttime [7–9]. The observed association between altered rest–activity rhythm and subjectively reported sleep problems in two independent cohorts of patients with metastatic colorectal cancer [10,11] further supported the hypothesis that disruption of circadian rhythms in cancer patients plays a role in the occurrence of sleep problems.

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Evidence from several epidemiological studies suggests that chronic circadian disruption is carcinogenic and associated with an increased risk of many cancers, including colorectal cancer [12,13]. Sleep disorders have also been reported to be associated with numerous adverse psychiatric and health outcomes, including: neurocognitive, metabolic, endocrine, and immune effects; increased fatigue; decreased physical activity; drowsiness; anxiety; depression; and an increased perception of pain [14–16]. These data point to circadian disruption as a potential mechanism for sleep problems and the associated health risks.

Despite this scientific evidence and the common knowledge of adverse health being associated with disturbed sleep, data on large populations of cancer patients are lacking with regard to the effects of sleep problems on clinical outcomes. Nonetheless, other patient-reported symptoms have been more extensively studied and their importance as independent prognostic factors in various cancers, including advanced colorectal cancer, has been confirmed [1,17–22].

The present study examined the prognostic role of subjective sleep complaints, before and during chemotherapy, in patients diagnosed with metastatic colorectal cancer. Data were obtained from a randomized controlled trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Chronotherapy Group.

2. Patients and methods

2.1. Study objective and design

The present clinical trial enrolled 564 patients, who were previously untreated for metastatic disease, from 36 centers in 10 countries between October 1998 and February 2002. A total of 282 patients were randomly assigned to one of the following treatment arms: FOLFOX2 or chronoFLO4 [23] (Fig. 1). Both regimens combined oxaliplatin, 5-fluorouracil, and leucovorin, administered with either a conventional, non-time-stipulated 2-day delivery (FOLFOX2), or with a chronomodulated, circadian-based infusion for four days (chronoFLO4). The description of these schedules, the patient inclusion and exclusion criteria, and the report of overall outcomes of the trial have been detailed elsewhere [23]. The study, which was approved by the EORTC protocol review committee and the ethics committee of each participating center, was conducted in compliance with the Helsinki declaration. All patients provided written informed consent.

2.2. Sleep assessment

Participants' subjective sleep was measured using the corresponding scale of a multidimensional questionnaire of HRQoL, the EORTC Quality of Life Questionnaire C30 (QLQ-C30) version 2.0 [24]. Assessments were performed at baseline (before chemotherapy start, but after a variable amount of time since initial cancer diagnosis and staging work-up) and during protocol chemotherapy (every fourth cycle of chemotherapy, about two months apart). The sleep score from EORTC QLQ-C30 was calculated using the recommended EORTC procedures [24] and involved the transformation of raw scores of increased severity into a linear scale ranging from 0 to 100. In particular, the EORTC QLQ-C30 questionnaire involves one straightforward question: '[During the past week] Have you had trouble sleeping?' It was considered that participants had no subjective sleep complaints if they answered 'not at all' (corresponding to 0 on the scale). The other values of the scale (ie, 33.3, 66.7 or 100, corresponding to 'a little', 'quite a bit' and 'very much', respectively) were considered as subjective reports of sleep problems.

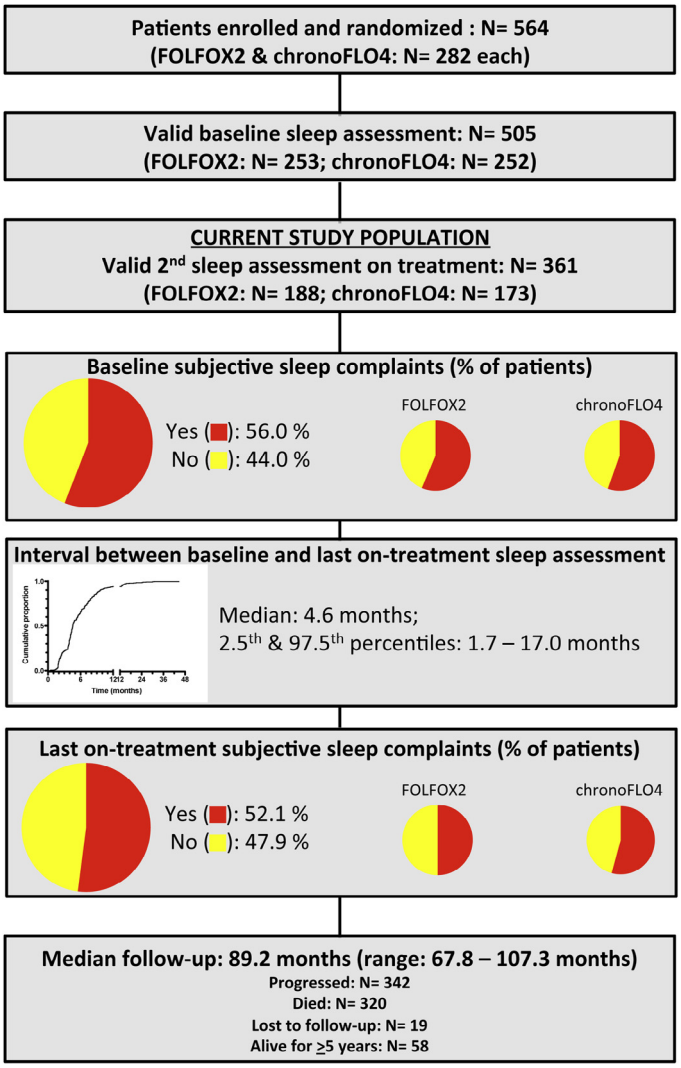

Fig. 1. Study flowchart.

2.3. Statistical analysis

The primary endpoint of the present study was the association between subjective sleep complaints and overall survival (OS). This association was explored by using sleep scores at baseline, while on treatment, and as time-dependent covariates (TDC). In each case, OS was measured from the date of completion of the corresponding questionnaire to the date of death (due to any cause). Participants still alive at the time of database locking were censored at the last date known to be alive. Similarly, time to progression (TTP) was calculated from the date of questionnaire completion until the date of disease progression or death, whichever occurred first.

Survival curves and probabilities were estimated using the Kaplan–Meier technique, and differences between survival curves were assessed using the log-rank test. The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival. For the prognostic analysis, the subjective sleep complaint was used either as a simple variable or as a time-dependent covariate. A multivariate prognostic model was then built, forcedly entering other possible prognostic factors. The added adjusting factors included: randomized treatment, age, sex, site of primary tumor, resection of primary tumor, Duke's stage at diagnosis, prior adjuvant chemotherapy, World Health Organization (WHO) performance status (PS) at baseline, number of metastatic

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sites, body mass index (BMI) at baseline, anemia, leukocytosis, and elevated alkaline phosphatases or lactate dehydrogenase (LDH) [25]. For survival analysis using sleep data during treatment, PS and BMI at day 1 of the corresponding chemotherapy cycle of questionnaire completion were used instead of baseline values. In this latter model, the number of chemotherapy cycles received was also entered in the final Cox model. All analyses were performed in the whole study population and, subsequently, in each treatment arm separately. Moreover, exploratory subgroup analyses were performed to observe differences in the prognostic significance of subjective sleep complaints on OS.

The best objective tumor response (OR) was assessed using WHO criteria. Univariate and multivariate binary logistic regression were used to assess the predictive role of baseline sleep complaints on response rate.

Baseline clinical and demographic factors associated with subjective sleep complaints were explored using a two-sided Chi-squared test (for categorical variables) or Wilcoxon *t*-test (for quantitative variables). The level of statistical significance was set at $p < 0.05$. All analyses were performed using PASW 16 software (SPSS Inc., USA).

3. Results

3.1. Demographics and biomedical characteristics of study participants

Out of the 564 enrolled participants, 361 (64%) had an available sleep assessment both at baseline and at least once during treatment. Demographics and biomedical characteristics in the current study population ($n = 361$) (summarized in Table 1) were comparable to those of the whole population of the EORTC 05963 trial (data not shown) [23].

The interval between baseline sleep assessment and the last HRQoL assessment while on treatment is shown in Fig. 1.

3.2. Prevalence of subjective sleep problems at baseline and on treatment

Prevalence of sleep problems is shown in Fig. 1. There were no differences between treatment arms concerning sleep problems reported at either baseline or during treatment.

Overall, 131 participants (36.3%) reported sleep problems at both assessments (baseline and while receiving treatment); no mention of sleep problems was recounted by 102 participants (28.3%) at both assessments. Fifty-seven participants reported new-onset sleep problems (15.8%), and 71 (19.7%) experienced sleep remission while receiving chemotherapy. These figures were comparable for participants on both FOLFOX2 and chronoFLO4 ($p = 0.74$, data not shown).

3.3. Clinical and demographic factors associated with subjective sleep problems

Out of the entire baseline clinical factors that were screened, only female gender ($p = 0.023$) and poor PS ($p = 0.002$) were significantly associated with baseline sleep problems (Table 1). Thus, sleep problems were more prevalent in females than in males, and in those with poorer PS, compared to those with better PS = 0, both at baseline and on treatment ($p = 0.018$ and $p = 0.01$, respectively).

3.4. Relationships between participant-reported sleep problems and clinical outcomes

The presence of subjective sleep complaints at baseline was associated with a 39% higher risk of earlier death (95% confidence interval [CI] 11% to 74%, $p = 0.0034$), a 44% higher risk of earlier disease progression (16% to 78%, $p = 0.0009$), and a 42% lower chance of obtaining an OR (complete or partial) (11% to 62%, $p = 0.011$) (Fig. 2). Thus, median OS in participants with sleep complaints

Table 1
Clinical and demographic features of the whole study population and with/without subjective sleep complaints at baseline.

Variable		Total study population ($n = 361$)	Sleep complaints at baseline	
			No ($n = 159$)	Yes ($n = 202$)
		Number (%)	Number (%)	Number (%)
Age	Median	62.0	61.1	62.2
	(range)	(22.3–75.9)	(34.5–75.5)	(22.3–75.9)
Randomized treatment	FOLFOX2	188 (52.1)	82 (51.6)	106 (52.5)
	chronoFLO4	173 (47.9)	77 (48.4)	96 (47.5)
Sex	Female	140 (38.8)	51 (32.1)	89 (44.1)
	Male	221 (61.2)	108 (67.9)	113 (55.9)
Primary tumor	Colon	348 (96.4)	155 (97.5)	193 (95.5)
	Resected	312 (86.4)	136 (85.5)	176 (87.1)
Prior adjuvant chemotherapy	Yes	67 (18.6)	31 (19.5)	34 (16.8)
Synchronous metastases	Yes	268 (74.2)	114 (71.7)	154 (76.2)
Number of metastatic sites	1	146 (40.4)	69 (43.4)	77 (38.1)
	2	133 (36.8)	52 (32.7)	81 (40.1)
	≥3	82 (22.7)	38 (23.9)	44 (21.8)
PS (WHO)	0	180 (49.9)	96 (60.4)	84 (41.6)
	1	147 (40.7)	52 (32.7)	95 (47.0)
	2	34 (9.4)	11 (6.9)	23 (11.4)
Body Mass Index (kg/m^2)	Normal (18.5–24.9)	181 (50.1)	73 (45.9)	108 (53.5)
	Abnormal (<18.5 or >25.0)	180 (49.9)	86 (54.1)	94 (46.5)
Baseline biology	Hb <12 g/dL	144 (39.9)	60 (37.7)	84 (41.6)
	WBC >10× 10^9/L	84 (23.3)	31 (19.5)	53 (26.2)
	ALP >300 IU/L	82 (22.7)	34 (21.4)	48 (23.8)
	LDH >2× ULN	127 (35.2)	55 (34.6)	72 (35.6)

ALP, Alkaline Phosphatases; Hb, Hemoglobin; LDH, Lactate Dehydrogenases; PS (WHO), Performance Status; WBC, white blood cells; ULN, Upper Limit of the Norm.

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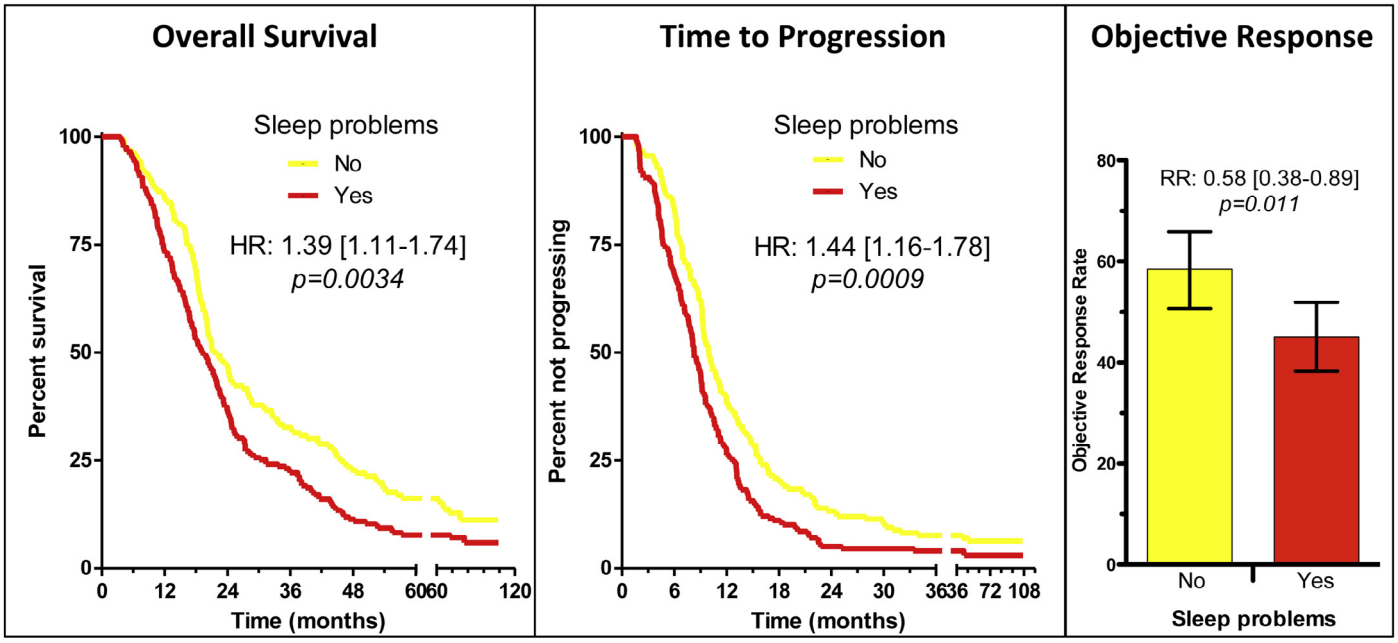

Fig. 2. Clinical outcomes according to baseline sleep complaints (red, yes; yellow, no). Left panel: Kaplan–Meier curves for overall survival. Middle panel: Kaplan–Meier curves for time to progression. Right panel: objective response rate (complete and partial, WHO criteria), with 95% CI. HR, hazard ratio; OR, odds ratio. Results presented for univariate analyses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

at baseline was 19.1 months (95% CI 16.6 months to 21.7 months), compared to 21.7 months (18.6 months to 24.8 months) in those not reporting sleep complaints at baseline. Similarly, median TTP was 8.3 (7.5 to 9.0) and 10.0 months (8.9 to 11.1), respectively, in participants with and without sleep problems at baseline. Finally, the OR rate was 45.1% (95% CI 38.3% to 51.9%) among those with sleep problems at baseline, compared to 58.5% (50.7% to 65.9%) in those without sleep problems at baseline (Fig. 2).

Persisting or newly appeared sleep complaints during treatment were significantly associated with shorter survival. In participants with sleep problems, median OS was 14.1 months (12.6 to 15.5), compared to 15.8 months (13.2 to 18.4) in patients without sleep problems (data not shown, HR 1.27, 95% CI 1.02 to 1.58, $p = 0.036$). Moreover, when subjective sleep complaints were considered as time-dependent covariates, their presence predicted significantly shorter OS (HR 1.30, 95% CI 1.05 to 1.63, $p = 0.019$).

Following adjustment for other known prognostic factors, baseline sleep problems remained independently and significantly associated with shorter OS, with an estimated 36% (95% CI 7% to 72%) increased risk of an earlier death ($p = 0.011$) (Table 2). The final model included baseline PS, number of metastatic sites, and elevated LDH values (Table 2). Similarly, baseline sleep problems remained in the multivariate models, independently predicting both shorter TTP (HR 1.43, 95% CI 1.13 to 1.79, $p = 0.002$) and lower OR rate (RR 0.58, 95% CI 0.37 to 0.90, $p = 0.016$) (data not shown).

The multivariate model, with sleep problems considered as the time-dependent covariate, confirmed the independent prognostic value of participant-reported altered sleep on OS, with an estimated increased risk roughly unchanged following adjustment for other possible prognostic factors (HR 1.37, 95% CI 1.08 to 1.72, $p = 0.008$) (Table 2). The other variables in the final models were the same as in the previous one (ie, baseline PS, number of metastatic sites and LDH) (Table 2).

Conversely, the presence of sleep problems at the last available assessment while on treatment protocol was not associated with an independent and significantly higher risk of earlier death ($p = 0.234$). The main prognostic factor was PS at the date of the last

Table 2
Final multivariate proportional Cox regression hazard models for overall survival with subjective sleep complaints at baseline, on treatment, and as a time-dependent covariate, in the whole study population.

Variable		HR (95% CI)	p
At baseline			
Sleep complaints	No	1	0.011
	Yes	1.36 (1.07–1.72)	
PS (WHO)	0	1	0.010
	1	1.33 (1.03–1.72)	
	2	1.91 (1.22–2.99)	
Number of metastatic sites	1	1	<0.0001
	2	1.52 (1.15–2.00)	
	≥3	3.05 (2.21–4.20)	
LDH	≤2× ULN	1	0.016
	>2× ULN	1.33 (1.02–1.75)	
	Unknown	1.69 (1.11–2.57)	
On treatment			
Sleep complaints	No	1	0.234
	Yes	1.16 (0.91–1.48)	
Number of metastatic sites	1	1	<0.0001
	2	1.49 (1.12–1.98)	
	≥3	2.73 (1.96–3.82)	
LDH	≤2× ULN	1	0.010
	>2× ULN	1.45 (1.09–1.93)	
	Unknown	1.66 (1.09–2.55)	
PS (WHO) (at day 1 of the cycle of last questionnaire)	0	1	<0.0001
	1	1.62 (1.22–2.15)	
	2	2.18 (1.37–3.47)	
	3	9.70 (1.24–76.1)	
As time-dependent covariate			
Sleep complaints	No	1	0.008
	Yes	1.37 (1.08–1.72)	
PS (WHO) (at baseline)	0	1	0.002
	1	1.41 (1.09–1.82)	
	2	2.09 (1.34–3.26)	
Number of metastatic sites	1	1	<0.0001
	2	1.51 (1.15–1.98)	
	≥3	3.01 (2.19–4.14)	
LDH	≤2× ULN	1	0.013
	>2× ULN	1.40 (1.06–1.84)	
	Unknown	1.64 (1.08–2.49)	

LDH, Lactate Dehydrogenases; PS (WHO), Performance Status; ULN, Upper Limit of the Norm.

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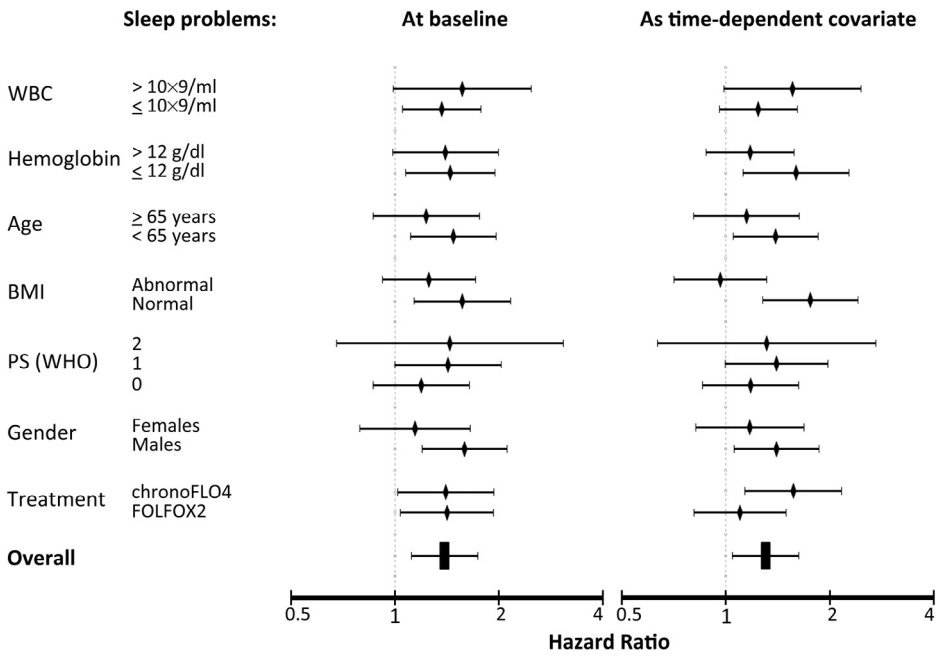

Fig. 3. Forrest plot for overall survival, indicating the hazard ratio (and 95% CI) of an earlier death, obtained with univariate Cox proportional regression hazard models, according to the presence of subjective sleep complaints either at baseline (left panel) or as a time-dependent covariate (right panel).

questionnaire completion, along with the number of metastatic sites and LDH (Table 2).

Overall, exploratory subgroup analyses showed a consistently increased risk for an earlier death in all subgroups tested that were associated with subjective sleep complaints, whether used as a simple variable or as a time-dependent covariate (Fig. 3).

3.5. Differences of survival prognostic models according to treatment arm

Participants with subjective reports of sleep problems at baseline displayed significantly shorter survival, regardless of the treatment schedule that they subsequently received. Indeed, on FOLFOX2, the median OS was 17.7 months (15.8 to 19.5) in participants reporting sleep problems and 22.6 months (15.9 to 29.3) in those without sleep problems. Respective corresponding median OS values on chronoFLO4 were 20.9 months (17.8 to 24.0) and 21.3 months (18.5 to 24.1) (Fig. 4). This translated into a highly similar hazard ratio for earlier death (HR 1.41, 95% CI 1.04 to 1.93, $p = 0.029$ on FOLFOX2; HR 1.40, 95% CI 1.02 to 1.93, $p = 0.04$ on chronoFLO4, respectively). In multivariate analyses, baseline subjective sleep problems were associated with a significant shorter survival only in patients receiving chronoFLO4 ($p = 0.012$) (Table 3). In participants receiving FOLFOX2, the survival difference was approaching statistical significance ($p = 0.056$) (Table 3).

Subjective sleep problems observed at the last valid assessment while on treatment were significantly associated with a shorter survival in those on chronoFLO4 ($p = 0.009$), and not in those treated with FOLFOX2 ($p = 0.75$) (Fig. 4; Table 3). Thus, median OS was similar in participants on FOLFOX2, regardless of the occurrence (13.6 months, 95% CI 11.7 to 15.6) or not (15.0 months, 11.6 to 18.3) of sleep problems while on treatment ($p = 0.75$). Meanwhile, OS was significantly longer in patients without sleep problems (16.7 months, 11.9 to 21.5) as compared to those complaining of having sleep problems (14.5 months, 11.9 to 17.1) while receiving chronoFLO4 ($p = 0.009$) (Fig. 4). However, on multivariate analysis, this survival difference did not reach statistical significance ($p = 0.088$) (Table 3).

This difference between treatment regimens and the effect of subjective sleep problems on OS while on treatment was confirmed by the time-dependent covariate analysis, showing a significant association between sleep problems with shorter OS on chronoFLO4 ($p = 0.006$), but not on FOLFOX2 ($p = 0.54$) (Table 3). In participants treated with chronoFLO4, subjective sleep problems, treated as a time-dependent covariate, independently predicted earlier death, even after adjusting for other possible prognostic factors ($p = 0.001$) (Table 3).

Table 3
Univariate and multivariate hazard ratios (95% Confidence Interval) for overall survival of subjective sleep complaints at baseline, on treatment, and as a time-dependent covariate, separately in the FOLFOX2 and chronoFLO4 treatment arms.

Subjective sleep complaints (yes)	FOLFOX2				chronoFLO4			
	Univariate		Multivariate		Univariate		Multivariate	
	HR	*p*	HR	*p*	HR	*p*	HR	*p*
At baseline	1.41 (1.04–1.93)	**0.029**	1.40 (0.99–1.97)	0.056	1.40 (1.02–1.93)	**0.040**	1.60 (1.11–2.32)	**0.012**
On treatment	1.05 (0.78–1.43)	0.75	1.20 (0.82–1.74)	0.35	1.53 (1.11–2.11)	**0.009**	1.38 (0.95–2.01)	0.088
As time-dependent covariate	1.10 (0.81–1.49)	0.54	1.27 (0.90–1.78)	0.18	1.57 (1.14–2.17)	**0.006**	1.74 (1.24–2.44)	**0.001**

In bold: significant p values (< 0.05).

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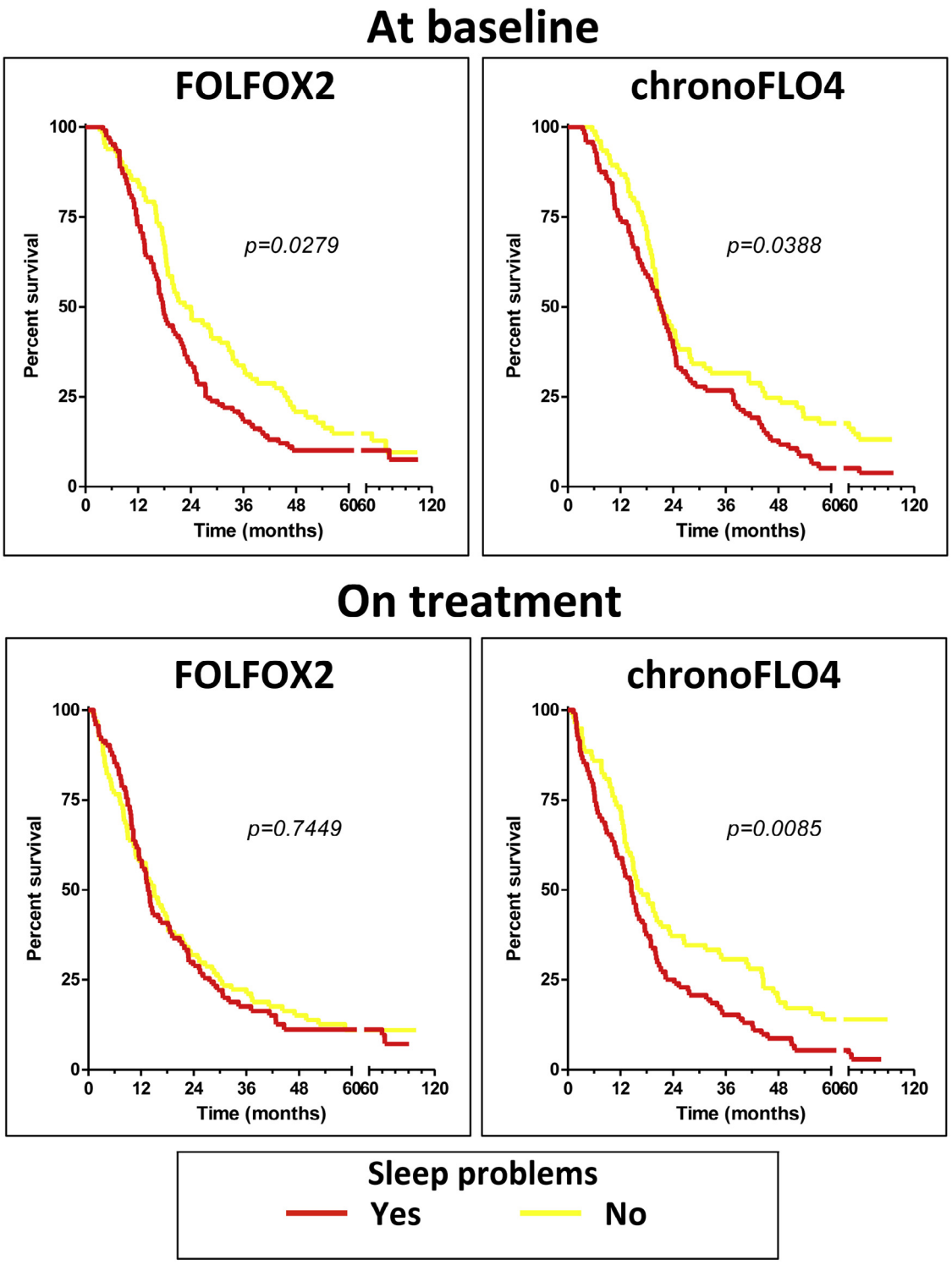

Fig. 4. Kaplan–Meier curves for overall survival in patients on FOLFOX2 (left panels) or on chronoFLO4 (right panels), according to sleep complaints (red, yes; yellow, no) at baseline (top panels), or at the last assessment while on treatment (bottom panels). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In the present study, it was shown for the first time that reported good sleep, as measured using a single subjective questionnaire item, was associated with better clinical outcomes in participants with metastatic colorectal cancer. It was found that 44% of those who reported no sleep complaints before chemotherapy treatment (but after diagnosis of metastatic disease) had a median 2-month increase in overall survival and time to progression. In addition, these people had an objective response rate about 13.5% higher than those complaining of sleep problems. These positive prognostic effects of good sleep remained significant, even after adjusting for other known prognostic factors or subgroups. These results further emphasize the clinical relevance of poor sleep in cancer

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patients, which has previously been associated with fatigue, mood disorders, poor functioning, and worse quality of life [14,15]. Sleep problems, however, remain an overlooked issue in cancer patients, despite the known negative effects of poor sleep quality and quantity in cancer-free populations, where they represent a relevant social and health issue [26–28].

The present study did not examine the potential mechanism of action behind sleep and survival. Sleep–wake cycles and circadian rhythms, especially those of rest and activity, are closely linked [1,29]. An alteration of the circadian rest–activity rhythm has been shown to be an independent negative prognostic factor in survival in three separate studies involving patients with advanced colorectal cancer [10,11,30,31]. These studies have also confirmed the correlation between subjective sleep complaints (measured with the single item of the EORTC questionnaire), and a clinically relevant circadian actigraphy parameter – the dichotomy index I < O [10,11]. As such, the current findings are in agreement with the hypothesis that altered sleep (and circadian function), either before the start of treatment or during chemotherapy, are associated with poorer outcomes in cancer patients [32], and in good agreement with experimental evidence in laboratory animals [33]. Furthermore, a recent clinical study further found that objectively measured poor sleep efficiency was an independent poor prognostic indicator for survival in advanced breast cancer patients [34]. Thus, the present findings support the clinical relevance of regular circadian rhythms, including sleep–wake cycles, in advanced cancer patients undergoing treatment [32].

The subgroup analyses furthermore substantiate the hypothesis that excessive toxicity could hamper the efficacy of circadian-based chronomodulated chemotherapy [8,30,32,33,35,36]. In the present study, it was found that the complaint of sleep troubles at the last on-treatment assessment was correlated with shorter OS in patients treated with chronoFLO4, but not with FOLFOX2. Analysis using sleep problems as a time-dependent covariate confirmed that the negative prognostic value of sleep complaints was limited to participants on chronoFLO4. Thus, the findings underscore the hypothesis that optimal efficacy of circadian-based chronotherapy is associated with optimal tolerability [32,33,37]. Indeed, the persistence of robust circadian function during chemotherapy, which is a recently documented phenomenon [38], is associated with lower incidence and/or severity of chemotherapy toxicity, and has been shown to predict for better efficacy of chronotherapy [8,30,32,33,35,36]. Thus, as for severe neutropenia or clinically meaningful fatigue and/or weight loss, subjective sleep complaints during treatment might reflect disrupted circadian function and decrease chronotherapy effectiveness.

In the present study, subjective sleep complaints were screened by using an item from a validated and widely used HRQoL questionnaire, with translations available in every suitable language for the study population [24,39]. The EORTC QLQ-C30 evaluates sleep with a single question and is part of a multidimensional patient-rated questionnaire. Given the various forms of possible sleep troubles, the use of a single item, although validated for this assessment, constitutes a limitation of this study. Another limitation is the compliance rate, which was suboptimal, as only 64% of participants provided sleep data for the present study.

The strengths of the present study include a large sample size, the prospective collection of data, and a homogeneous population of patients previously untreated for metastatic disease. The present findings are in agreement with recent results in women with advanced breast cancer [34], and provide insight into the relationship between sleep, circadian rhythms, chemotherapy toxicity, and clinical outcomes in cancer patients.

Disturbed sleep is related to circadian disruption, and both sleep disorders and circadian disruption have detrimental effects on immunity and metabolic processes [14,28,32,37,40]. The alleviation of sleep complaints through behavioral and/or pharmacologic interventions could potentially improve circadian function, and jointly enhance both quality of life and survival. Therefore, future research is warranted in an attempt to improve sleep and circadian function in cancer patients, using cognitive-behavioral approaches and/or chronobiotic agents [15,32].

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.10.022.

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